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Effect of Increasing Concentrations of Xanthan Gum, HPMC K15 and Sodium Alginate on the Release Kinetics of Acyclovir Sustained Release Tablet

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ABSTRACT

The present research paper focuses on designing not only the sustained release tablets of acyclovir to ensure time-dependent, sustained release formulation but also studying the effect of sodium alginate, Xanthan gum and HPMCV K15 on the in vitro release profile of the tablet. The initial release of drug from these matrices occurs by the drug dissolution in the water penetrated into the matrix. The overall drug release from these matrices is governed by hydration, gel layer formation and drug diffusion into the gel layer and to the dissolution media. The formulations ACL1 to ACL5 are containing 200mg of drug with a combination of different excepients. The drug release showed in ACL1 was 95.78%, for only 10hrs and ACL2 showed 90.66% within 11hrs because there was less presence of Xanthan Gum. The Acyclovir tablets of ACL3 showed 91.35% in 12hrs, ACL4 and ACL5 showed drug release of 95.33% for 8hrs and 95.85% for 9hrs. In further formulations the dose of Acyclovir was increased to 400mg ACL6 to ACL10 that are containing combination of excipients. The drug release for the formulations ACL6 showed a drug release of 97.44% for 10hrs and ACL7 showed a drug release 92.4% for 11hrs. From these twelve formulations it was concluded that increase in concentration of Xanthan Gum and Sodium alginate overrun the effect of HPMC K15. The dissolution characteristics allowed for drug to be released in a controlled manner, highlighting the importance for the correct selection of polymers according to their physical, mechanical and pharmacokinetic properties.

Keywords: sodium alginate, Xanthan gum, HPMCV K15, dissolution characteristics, sustained release

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INTRODUCTION

Acyclovir is an antiviral agent which is active in vitro against Herpes simplex (HSV) types I and II and Varicella zoster virus (VZV). However, the relationship between in vitro sensitivity of herpes viruses to Aciclovir and clinical response to therapy has yet to be established. Acyclovir needs to be phosphorylated to the active compound, aciclovir triphosphate, in order to become active against the virus. Such conversion is very limited in normal cells and in addition cellular DNA polymerase is not very sensitive to the active compound. [1-3]

The ideal half-life for preparing the sustained release dosage form should range from 3 to 8 hours. Unstable plasma half life depending upon absorption is 2.9 to 3.3 hrs makes acyclovir an ideal candidate for Sustained release tablets. The oral doses of Aciclovir for adults range from 200 mg every 4 h (while awake) to 800 mg three times a day for 5–10 days. For chronic suppression of recurrent infections, the dose is 400 mg twice a day. The oral dose for treatment of chickenpox and herpes zoster is 800 mg aciclovir every 4 h for 5–10 days. Further the dosing is non patient compliant. Although Intravenous route is preferred for the drug owing to its low bioavailability (15-30%), but owing to its toxicities there occurs a need of Sustained release or extended release dosage form to overcome hurdles of plasma profile fluctuations. The present study tries to optimize the polymeric ratios and variables which are required not only for drug dissolution but also determine the mechanism of drug release. The formulations are designed in arithmetic progressions of MCC and Xanthan Gum, whereas sodium alginate and HPMC are proportional to the dose. The effects of concentration on mechanism of drug release are studied and the best formulation is understood.

MATERIALS AND METHODS

The objective of the proposed work was to design and develop sustained release tablets of the given drug and to ensure time-dependent, sustained release formulation with optimizing the process variables and perform pre-formulation studies[4] . To evaluate the drug content, in vitro drug release kinetics of the drug as per the design of the experiment. Different drug solubility's is considered, as highly soluble drugs will dissolve immediately after administration. Reduced drug solubility increases the tendency of the tablet to erode due to particle displacement. The aim of the formulation is that, the drug should have a short half-life. If a drug has a long half-life then there is a risk of accumulation as it will be eliminated at a slower rate compared to its absorption. A drug that is tested in-vitro needs to be able to provide similar release characteristics once administered and is under patho-physiological or in-vivo conditions. A direct correlation of in-

vitro data with in-vivo release is not possible without thorough and careful analysis. For example, there is a difference in the availability of water in different parts of the gastrointestinal tract and such factors need to be considered when designing tablets for extended release. The dissolution characteristics should allow for drug to be released in a controlled manner, highlighting the importance for the correct selection of polymers according to their physical, mechanical and pharmacokinetic properties. The first step before formulating a tablet is the preformulation. Preformulation is defined as the phase of research and development process where physics, chemical and mechanical properties of a new drug substance are characterized alone and when combined with excipients in order to develop stable, safe and effective dosage form. A thorough understanding of physicochemical properties may ultimately provide a rationale for formulation design or support the need for molecular modification or merely confirm that there are no significant barriers to the compound development. Hence, preformulation studies were performed on the obtained sample of drug for solubility analysis, identification and compatibility studies.

Solubility analysis

Preformulation solubility analysis was done, which include the selection of suitable solvent, to dissolve the respective drug as well as various excipients. The solubility was performed visually by dissolving in suitable solvents and water. The available literature on solubility profile of Acyclovir indicated that the drug is very soluble in methanol, DMSO, dioxane and ethanol and practically insoluble in water.

Melting point determination:

Melting point is the temperature at which the pure liquid and solid exist in equilibrium. In practice, it is taken as equilibrium mixture at an external pressure of 1 atmosphere; this is sometimes known as normal melting points. The Thiel's tube method of melting point determination in liquid paraffin was used in the present study.

DRUG-EXCIPIENTS COMPATIBILITY STUDIES

Compatibility of drug (Acyclovir) and polymers which are used to prepare tablets was established by infrared absorption spectral analysis

FTIR Spectral analysis

IR spectral analysis of pure drug Acyclovir, and excipients was carried out and observation was made whether changes in chemical constitution of drug after combining it with the polymers occurred. The samples were crushed with KBr to get pellets by applying pressure of 600 Kg/cm^2.

Infra Red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug.

Differential scanning calorimetry (DSC) studies

Thermograms were obtained by using scanning colorimeter (Netzsch, 200F) ata heating rate 10°c/min. over a temperature range of 35-500°c. The sample was hermetically sealed in an aluminum crucible. Nitrogen gas was purged at rate of 10 ml/min. for maintaining inert atmosphere.

Calibration curve for Acyclovir and determination of λ_{max} of Acyclovir

The calibration curve for Acyclovir was prepared by using PBS 6.8 pH. The λ_{max} of pure Acyclovir drug was determined using the UV Spectrophotometer and solvent as water.

Evaluation of Pre Compression Parameters of Acyclovir SR Tablets

For a drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug.

Determination of bulk density and tapped density

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the following formulas:

$$\text{Bulk density} = W / V_o$$

$$\text{Tapped density} = W / V_F$$

Where, W = weight of the powder, V_O = initial volume, V_F = final volume

Flow Properties

Angle of repose of different formulations was measured by fixed funnel standing method. Granules were weighed and passed through the funnel, which was kept at a certain height from horizontal surface. The passed microspheres formed a pile of height 'h' above the horizontal surface and the pile was measured.[65] The angle of repose was determined by

$$\mathbf{Tan\ (\theta) = h / r}$$

$$\text{Angle of repose } (\theta) = \text{Tan}^{-1} (h / r)$$

Where h is the height of pile and r is radius

Compressibility Index and Hausner's Ratio

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size of a powder. The compressibility of a material can be estimated from the tap and bulk density

measurements. It is represented as percentage. In theory, the less compressible material is more flowable. Compressibility index were calculated using the formula

$$\text{Compressibilty}[\%] = \frac{\text{Tapped density} - \text{Bulk density}}{\textit{Tapped density}} \times 100$$

FORMULATION OF ACYCLOVIR SR TABLETS (WET GRANULATION METHOD)

The Sustained Release tablets were prepared by Wet granulation method**;** all the ingredients were weighed and mixed one by one according to the composition. First the drug, Lactose, Eudragit, HPMC were added to the mortar and pestle. Thorough mixing was done and the ingredients were passed through #40 mesh**.** Blended with water to form a damp mass and passed through #20mesh and dried at 40ºc and lubricants were added. Then the powder blend was compressed on a 9 Station Rotary compression machine by using 8mm circular shape punches.

Table 1: Formulation of Acyclovir Sustained release tablets

Formula. Code	Drug ACY	SA	XAN	HPMC K 15	MCC	Talc	MAN	Total
ACY1	400	20	20	15	20	10	QS	550
ACY2	400	20	40	15	21	10	QS	570
ACY3	400	20	80	15	22	10	QS	590
ACY4	400	20	120	15	23	10	QS	610
ACY5	600	30	30	20	24	10	QS	750
ACY6	600	30	60	20	25	10	QS	780
ACY7	600	30	90	20	26	10	QS	810
ACY8	600	30	120	20	27	10	QS	840
ACL9	800	40	30	20	28	10	QS	950
ACL10	800	40	60	20	29	10	QS	980
ACL11	800	40	90	20	30	10	QS	1010
ACL12	800	40	120	20	31	10	QS	1040

Evaluation of post compression parameters for Acyclovir Sustained Release Tablets

Thickness

Thickness of the Acyclovir was important for the uniformity of tablet. Thickness was measured using the Vernier callipers.

Hardness

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester.

Friability

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablet was

determined by using Veego Friabilator as per IP procedure of friability. It is expressed in percentage (%).

Swelling Index

The diameter of tablets was taken at intervals of five minutes until maximum diameter was attained with a digital Vernier caliper. Thereafter the swelling indices (SI) were calculated from initial diameter of tablet (D1) and maximum diameter on swelling in water (D2) as expressed below:

$$SI\ (\%) = D2/D1 \times 100$$

IN-VITRO DRUG RELEASE STUDIES

In-vitro dissolution studies of Acyclovir tablets were performed using USP type-II (Paddle) Type dissolution test apparatus. 600ml of buffer is used as a dissolution medium. The medium was maintained at 37±0.5ºC at a speed of 50rpm. The *in vitro* dissolution studies were performed at two different pH in 0.01N HCL for 2 hrs. An accurately weighed sample was responded in dissolution medium consisting 900ml of buffer and dissolution was done up to 12hrs.At prefixed time intervals (every 1 hour); 5ml of sample was withdrawn and filtered through 0.4 µm membrane filter. The volume of the dissolution medium was adjusted to 900ml at every sampling time by replace same 5ml of dissolution medium. Then the samples were analyzed Spectrophotometrically at 451nm.

RESULTS AND DISCUSSIONS

The objective of the proposed work was to design and develop sustained release tablets of the given drug and to ensure time-dependent, sustained release formulation with optimizing the process variables and perform pre-formulation studies. The results and observations are as follows:

Organoleptic Characteristics of Acyclovir

Table 1: Organoleptic Characteristics of Acyclovir

Properties	Result
Odour	Odourless
Colour	white
Form	Crystalline

Melting point of Acyclovir

Table 2: Melting point of Acyclovir

Sample	Reported	Observed
Acyclovir	255^0C	255.9^0C

Solubility analysis:

The solubility was performed visually by dissolving in suitable solvents and water. The available literature on solubility profile of Acyclovir indicated that the drug is very soluble in methanol, DMSO, dioxane and ethanol and practically insoluble in water. Acyclovir was found to be soluble in methanol, ethanol and DMSO. The study was carried out to select suitable dissolution medium for *in-vitro* release studies.

Standard curve of Acyclovir in PBS pH6.8

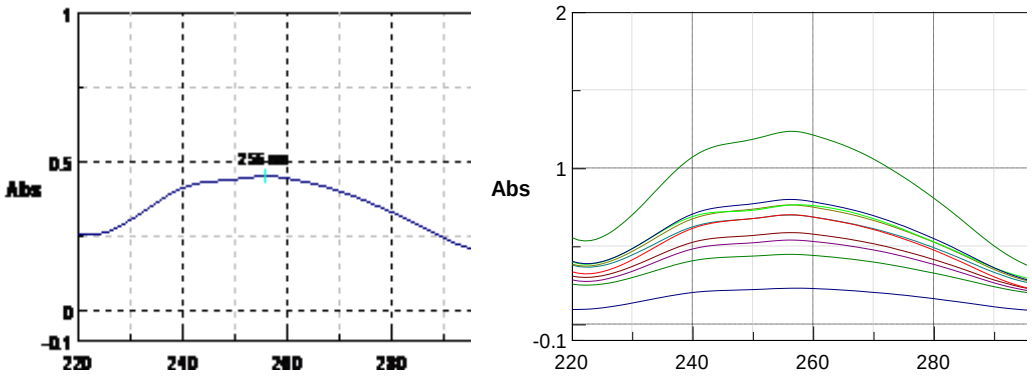

Figure 1: λmax and overlay spectrum of acyclovir in pH 6.8 at 256nm

Table 3 : Observations for Standard graph of Acyclovir in pH 6.8 at 256nm

Concentration (µg/ml)	Absorbance (236nm) in pH 6.8
2	0.185
4	0.312
6	0.403
8	0.531
10	0.604
12	0.705
14	0.769
16	0.874
18	0.978
20	1.18

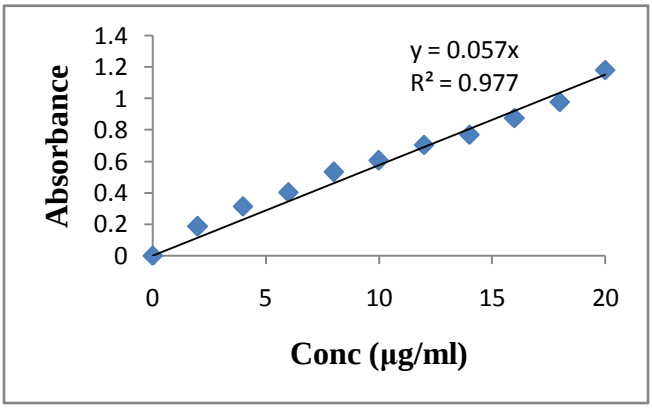

Figure 2: Calibration curve of Acyclovir in pH 6.8 at 256nm

Drug-excipient compatibility study (FT-IR spectral analysis)

The development of a successful formulation depends only on suitable selection of excipients. Hence the physical state of the drug Acyclovir and the excipients, Xanthan Gum, HPMC, Sodium Alginate, MCC, Talc and Mannitol individually and the combination of drug and polymers used for tablets preparation were studied by FTIR (Fourier transform infra red spectroscopy) to know the drug – polymer compatibility. The FTIR Spectrum of Pure acyclovir showed peaks at 3563.81 cm-1(O-H stretching), 1608.63cm-1 (O-H deformation), 3444.24 cm-1 (10 N-H stretching), 2927.94 cm-1 (aliphatic C-H stretching anti symmetric), 2856.06 cm-1 (aliphatic C-H stretching symmetric), 1482.99 cm-1 (aliphatic C-H deformation), 1714.41 cm-1 (C=O stretching) and 1143.8 cm-1 (C-O stretching). Therefore, there was no alteration and no interaction was observed between excipients and drug in combination. All the characteristic peaks of Acyclovir were present in combination, thus indicating compatibility between drug and excipients and finally confirm that there was no chemical modification of drug.

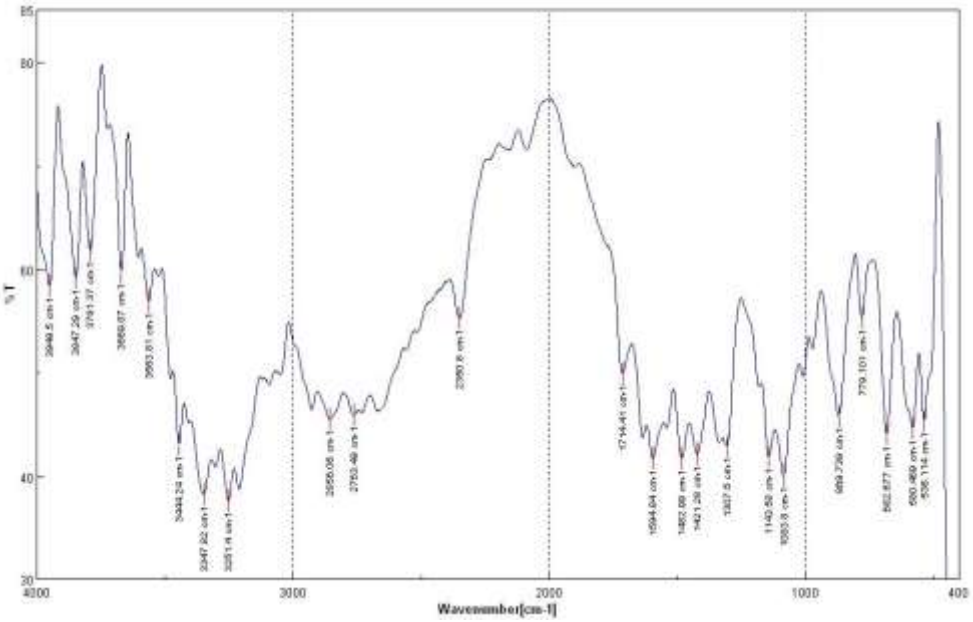

Figure 3: FTIR Spectrum of Pure Acyclovir

DSC studies:

DSC thermo grams of Acyclovir along with their combination of drug excipients have been shown. In case of Acyclovir two endothermic peaks were observed one at 197^0C, which corresponds to melting process and the other at 236^0C due to thermal decomposition. Combination of drug and excipients showed endothermic peak at 169.2 ^{0}C, it may be concluded that the drug has not shown any interaction with different excipients used in preparing the different formulations.

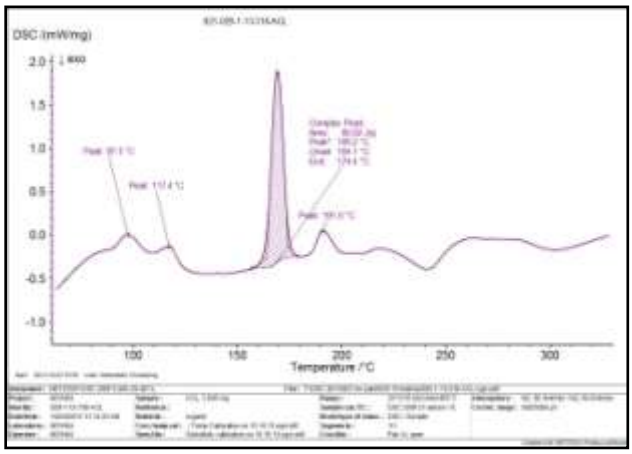

Figure 4: DSC thermo grams of Acyclovir along with their combination of drug excipients

EVALUATION OF PRE-COMPRESSION PARAMETERS OF ACYCLOVIR MATRIX TABLETS

The bulk density, tapped density, Hausner's ratio, Compressibility index and angle of repose for the blend was performed and reported in the Table 5. The bulk density for Acyclovir blend of entire formulations varied from 4.56±0.006 to 7.89±0.583. Tapped density for Acyclovir blend was varied from 4.99±0.066 to 9.11±0.75 respectively. Bulk density and Tapped densities showed good packability of the granules. For Acyclovir blend the compressibility index for all formulations ranges from 4.91±0.971 to 19.28±0.144 respectively. ACL7 has lowest Carr's index indicating good compressibility. The Hausner's ratio for Acyclovir blend ranges from 1.086±0.011 to 1.24±0.002. The ACL7 is having lowest Hausner's ratio indicating good flow property. Angle of repose for Acyclovir blends ranges from 21.16±0.921 to 28.49±0.572 respectively. These represents that the blend flows freely through the hopper.

Table 5: Powder Flow Properties for Acyclovir Sustained Release Tablets

S.No	F code	Bulk density ± S.D	Tapped density ± S.D	Hausner's ratio ±S.D	Carr's index± S.D	Angle of repose ± S.D
1	ACL1	4.57±0.015	5.097±0.058	1.116±0.01	10.393±0.78	24.83±0.865
2	ACL2	4.58±0.015	5.097±0.061	1.114±0.013	10.194±1.08	22.98±1.06
3	ACL3	4.56±0.006	5.653±0.011	1.24±0.002	19.28±0.144	22.813±0.949
4	ACL4	4.57±0.006	5.003±0.047	1.094±0.009	8.589±0.794	19.77±0.782
5	ACL5	4.58±0.011	4.99±0.066	1.088±0.011	8.079±1.0	24.37±0.754
6	ACL6	5.56±0.006	6.67±0.052	1.199±0.009	16.588±0.69	28.06±0.398
7	ACL7	5.58±0.01	6.06±0.053	1.086±0.011	7.915±0.93	23.617±0.647
8	ACL8	5.57±0.006	6.67±0.011	1.196±0.0008	16.4±0.058	26.49±0.65
9	ACL9	5.58±0.006	6.657±0.006	1.192±0.002	16.1±0.138	26.64±0.915
10	ACL10	5.58±0.01	6.64±0.011	1.19±0.001	16.01±0.077	21.16±0.921
11	ACL11	6.56±0.006	7.67±0.006	1.167±0.01	14.28±0.14	26.65±1.04
12	ACL12	6.56±0.006	7.64±0.006	1.164±0.011	14.13±0.122	27.75±0.813

The formulations ACL1 to ACL5 are containing 200mg of drug with a combination of different excepients. The drug release showed in ACL1 was 95.78%, for only 10hrs and ACL2 showed 90.66% within 11hrs because there was less presence of Xanthan Gum. The Acyclovir tablets of ACL3 showed 91.35% in 12hrs, ACL4 and ACL5 showed drug release of 95.33% for 8hrs and 95.85% for 9hrs. From these five formulations it was concluded that increase in concentration of Xanthan Gum there was a decrease in drug release. In further formulations the dose of Acyclovir was increased to 400mg ACL6 to ACL10 that are containing combination of excipients. The drug release for the formulations ACL6 showed a drug release of 97.44% for 10hrs and ACL7 showed a drug release 92.4% for 11hrs.

Table 8: Regression and Slope Data of Release Kinetics of Acyclovir SR Tablets

Formulation code	Mathematical models (release kinetics)				
	Zero order kinetics	First order kinetics	Higuchi's	Peppa's	
	r^2	r^2	r^2	r^2	n
ACL1	0.997	0.871	0.926	0.996	1.02
ACL2	0.998	0.915	0.928	0.997	0.939
ACL3	0.998	0.905	0.934	0.997	0.925
ACL4	0.995	0.797	0.877	0.999	1.12
ACL5	0.996	0.788	0.903	0.998	1.0
ACL6	0.996	0.847	0.932	0.996	1.02
ACL7	0.998	0.912	0.931	0.998	0.954
ACL8	0.997	0.88	0.94	0.995	0.916
ACL9	0.995	0.764	0.88	0.999	1.09
ACL10	0.994	0.715	0.898	0.997	0.975
ACL11	0.995	0.705	0.901	0.997	0.97
ACL12	0.996	0.929	0.941	0.985	1.0

Swelling Index

The diameter of tablets was taken at intervals of five minutes until maximum diameter was attained with a digital Vernier caliper[7, 8].

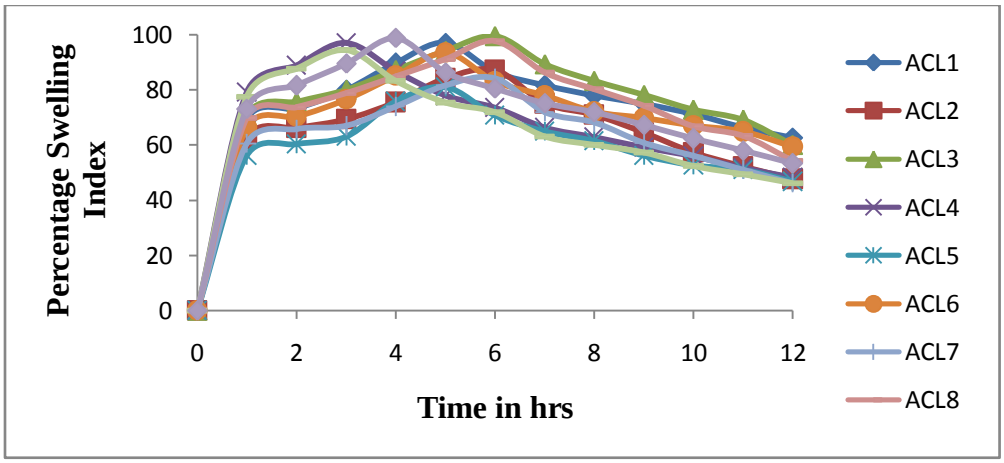

Figure 7: Swelling Index Plot for ACL1 to ACL12

Thereafter the swelling indices (SI) were calculated from initial diameter of tablet (D1) and maximum diameter on swelling in water (D2) as expressed below:

$$SI\ (\%) = D2/D1 \times 100$$

IN VITRO DISSOLUTION AND DRUG RELEASE KINETICS

The initial release of drug from these matrices occurs by the drug dissolution in the water penetrated into the matrix. The overall drug release from these matrices is governed by hydration, gel layer formation and drug diffusion into the gel layer and to the dissolution media. Polymer erosion also plays a major role in releasing drug from these matrices. These considerations indicate that hydrophilic polymers have the potential to sustain the release of drug from matrix tablets. The release of drug is retarded as concentration of gum increases in all formulation. In order to investigate the effect of polymer type and percentage on drug release profile, different formulations containing various percentages of Xanthan gum and Sodium alginate was used. All these natural gum is hydrophilic cellulose ether, which is used as a retarding release of drug in controllable manners up to 12 hrs.

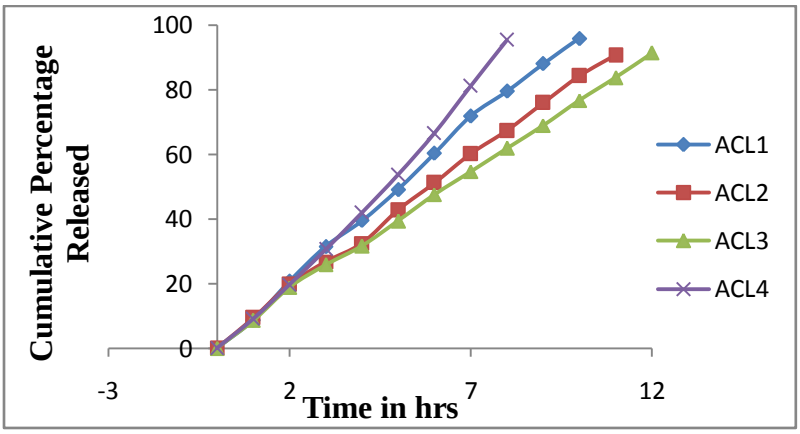

Figure 4: Zero order Release Plot for ACL1 to ACL4 SR Tablets

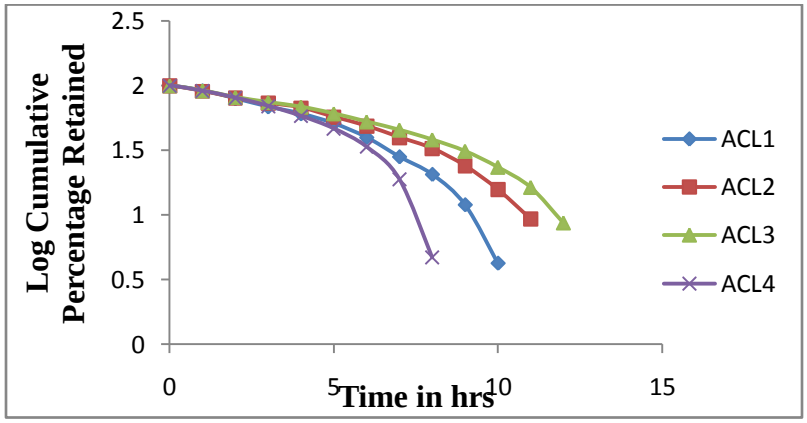

Figure 5: First order Release Plot for ACL1 to ACL4 SR Tablets

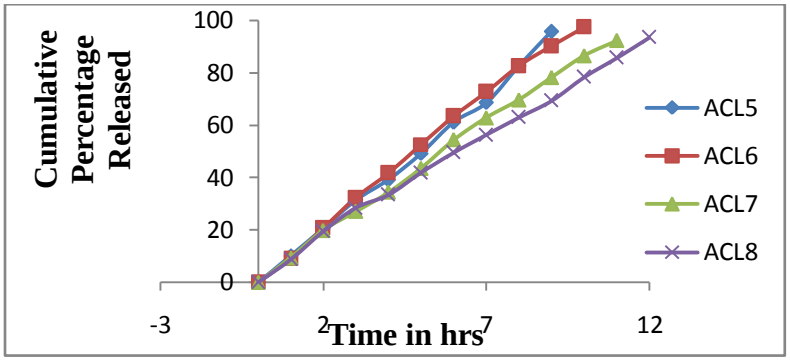

Figure 6: Zero order Release Plot for ACL5 to ACL8 SR Tablets

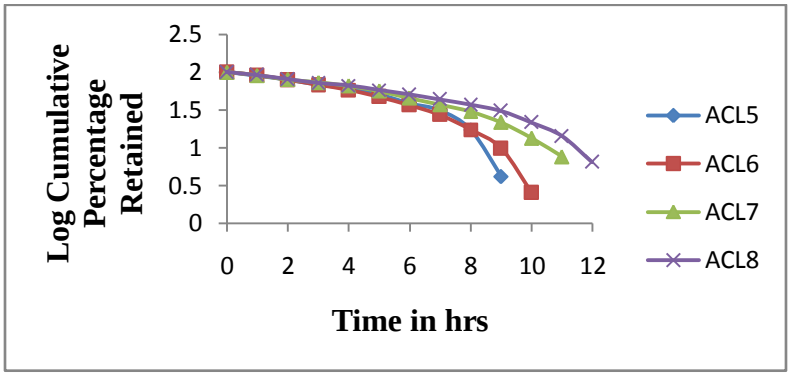

Figure 7: First order Release Plot for ACL5 to ACL8 SR Tablets

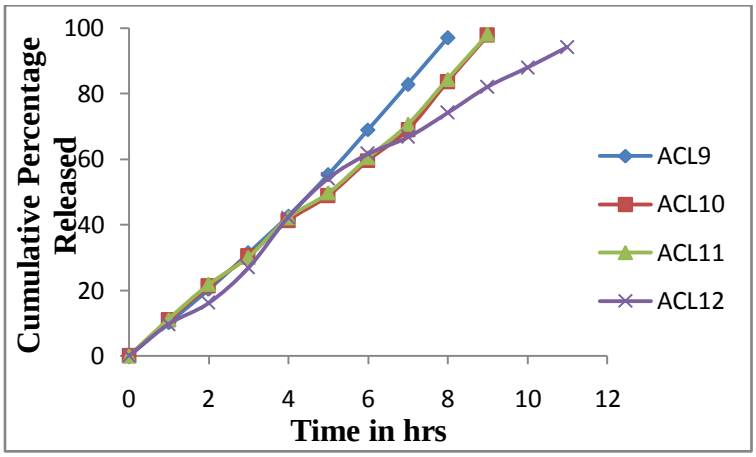

Figure 8: Zero Order Release Plot for ACL9 to ACL12 SR Tablets

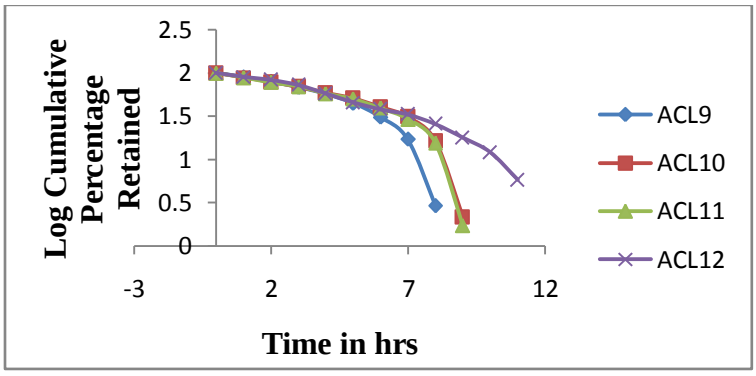

Figure 9: First Order Release Plot for ACL9 to ACL12 SR Tablets

So ACL3 was taken as a best formulation to achieve a prolonged maintenance of effective concentrations of drug for a period of 12hrs. The linear regression analysis of all the fabricated tablets shown as R2 values . When the data were plotted according to the first-order equation, for all formulations (ACL1 to ACL8) showed a fair linearity, with regression (R^2) values between (0.685 to 0.915) clearly indicate that drug was not release as per first order mechanism. All the formulation expressed by Higuchi classical diffusion equation as the plot shows linearity with regression coefficient (R2) value as (0.88 to 0.948) also not close to infinity indicate drug release process is not as per Higuchi plot. The zero-order plots of all formulations were found to be highly linear, and close to infinity as indicated by their high regression (R^2) values as (0.994 to 0.998). Therefore it was ascertained that the drug permeation from these formulations could follow either near zero or zero order kinetics. Hence release mechanism was shifted from zero order to Higuchi followed by first order kinetics.

CONCLUSION

Further, to understand the drug release mechanism, the data were fitted to Peppas equation. In the present study also it was observed, that n value was obtained between (0.91 to 1.12) for all formulation. These values suggesting that more than one mechanism may be involved in release kinetic. In the case of formulation ACL3 with Xanthan gum and sodium alginate shows non-fickian diffusion mechanism with n value as (0.925) therefore diffusion with erosion mechanism play role release from natural gum. It was clearly concluded that the drug release was governed with the combination of these natural polymers. When more quantity of sodium alginate was used rather than Xanthan gum there was a less sustaining effect and faster drug release as compared to combination of Xanthan gum because when matrices containing swellable polymers are exposed to dissolution medium, tablet surface becomes wet and hydrated to form a gel layer. It was also concluded that increase in dose with decrease in concentration of polymers or keeping constant in polymers ratio also effected the release of drug.

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